DOI:10.1046/j.1365-2125.2003.02000.x

Effect of omeprazole on the steady-state pharmacokinetics of voriconazole

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Aims Voriconazole, a novel triazole antifungal agent, is metabolized by the cytochrome P450 isoenzymes CYP2C19, CYP2C9, and to a lesser extent by CYP3A4. Omeprazole, a proton pump inhibitor used widely for the treatment of gastric and duodenal ulcers, is predominantly metabolized by CYP2C19 and CYP3A4. The aim of this study was to determine the effects of omeprazole on the steady-state pharmacokinetics of voriconazole. A secondary objective was to characterize the pharmacokinetic profile of an oral loading dose regimen of 400 mg twice-daily voriconazole on day 1.

Methods This was an open, randomized, placebo-controlled, two-way crossover study of 18 healthy male volunteers. Subjects received oral voriconazole (400 mg twice daily on day 1 followed by 200 mg twice daily on days 2–9 and a single 200-mg dose on day 10) with either omeprazole (40 mg once daily) or matched placebo for 10 days. There was a minimum 7-day washout between treatment periods.

Results Mean C_{max} and AUC_{τ} of voriconazole were increased by 15% [90% confidence interval (CI) 5, 25] and 41% (90% CI 29, 55), respectively, with no effect on t_{max} during coadministration of omeprazole. Visual inspection of predose plasma concentrations (C_{min}) indicated that steady-state plasma concentrations were achieved following the second loading dose. One subject withdrew from the study during the voriconazole + omeprazole treatment period because of treatment-related abnormal liver function test values. All other treatment-related adverse events resolved without intervention.

Conclusions Omeprazole had no clinically relevant effect on voriconazole exposure, suggesting that no voriconazole dosage adjustment is necessary for patients in whom omeprazole therapy is initiated. Administration of a 400-mg twice-daily oral loading dose regimen on day 1 resulted in steady-state plasma levels of voriconazole being achieved following the second loading dose.

Keywords: interaction, omeprazole, pharmacokinetics, safety, toleration, voriconazole

Introduction

Voriconazole is a triazole antifungal agent, developed as oral and intravenous formulations, with potent activity against a broad spectrum of clinically significant pathogens, including *Aspergillus* and *Candida* species [1–3], and emerging fungal pathogens, such as *Scedosporium* and *Fusarium* species [4, 5].

The pharmacokinetics of voriconazole have been investigated following single and multiple doses in healthy volunteers [6–8]. Voriconazole is extensively metabolized by the cytochrome (CYP) P450 system, mainly by the polymorphically expressed CYP2C19 isoenzyme, by CYP2C9, and to a lesser extent by CYP3A4 [9]. Because CYP2C19 is expressed polymorphically, individuals can be classified either as extensive metabolizers (EM) or poor metabolizers (PM). The PM phenotype is inherited as an autosomal recessive trait and interethnic differences in its distribution are well documented, with approximately 2–6% of Caucasians and about 20% of Asians being classified as PM [10, 11].

Omeprazole, a proton pump inhibitor, is indicated for duodenal and gastric ulcers, erosive oesophagitis, and gastroesophageal reflux disease, and acts by inhibition of gastric acid secretion [12]. Omeprazole is a competitive

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inhibitor of CYP2C19 [13, 14], and interactions with a number of drugs metabolized by the CYP P450 system have been reported, including diazepam, phenytoin and warfarin [12, 15]. Omeprazole is essentially completely metabolized *in vivo* to 5-hydroxy omeprazole and omeprazole-sulphone, with the formation of these pharmacologically inactive metabolites largely mediated by CYP2C19 and CYP3A4, respectively [16]. Further metabolism of omeprazole-sulphone to 5-hydroxy omeprazole-sulphone is also reported to be mediated by CYP2C19, thus both CYP2C19 and CYP3A are sequentially, but alternatively, involved in the metabolism of omeprazole [17]. The antifungal azole, ketoconazole, an inhibitor of CYP3A4, is known to inhibit the metabolism of omeprazole, especially in CYP2C19 PMs [18].

Considering the metabolic pathways, and the likelihood of patients requiring concomitant voriconazole and omeprazole therapy, the primary objective of this study was to investigate the pharmacokinetic interaction, safety, and toleration of omeprazole and voriconazole when coadministered to healthy volunteers. In addition, the study also investigated the use of a 400-mg twice-daily oral loading dose regimen, administered on day 1 only, to enable steady-state plasma concentrations to be achieved more rapidly.

Methods

Subjects

Healthy male volunteers, aged 18–45 years, weighing 60–100 kg, and with a body mass index within the permitted range of 18–28 [19], were randomized to receive study treatment following the provision of written informed consent. The study protocol was approved in writing by an independent Clinical Research Ethics Committee, Anatole France Street, Brussels, Belgium.

Volunteers with any evidence of clinically significant disease, allergy, drug sensitivity, or laboratory test results outside the normal ranges were excluded. Subjects were advised not to consume caffeine or other methylxanthines, grapefruit products or alcohol, or to take unaccustomed exercise during the 48 h prior to and for the duration of the study. If genotype was not already known, a single 5-ml blood sample was collected into an EDTA tube at the screening visit for CYP2C19 genotyping. Samples were stored at −20 °C and were transported in dry ice to Clinical Diagnostics, Genetics, and Measurements, Pfizer Central Research, Groton, USA, where individual CYP2C19 genotype status was determined using previously validated methods. At least two PMs for CYP2C19 were to be included in the study population.

Study design

This was an open, randomized, placebo-controlled, two-period, crossover study to investigate the effects of multiple-dose omeprazole on the steady-state pharmacokinetics of voriconazole. Each study period consisted of 10 days' treatment, separated by a minimum 7-day washout.

All subjects received oral voriconazole: 400 mg twice-daily loading dose (day 1), followed by a 200-mg b.d. maintenance dose regimen (days 2–9), and a single 200-mg dose only on the morning of day 10. Once-daily oral omeprazole (40 mg; Losec®; AstraZeneca Plc., London, UK), or matched placebo, was coadministered with the morning dose of voriconazole on days 1–10. Drugs were taken with 250 ml water, and food was prohibited within 1 h before and after each dose. All subjects were admitted to the study centre on the evening prior to day 1 of each period, and remained there until the morning of day 2. On days 2–9, morning doses of voriconazole and omeprazole or placebo were administered under supervision in the study centre. The subjects were provided with the evening dose of voriconazole to be taken at home. All subjects returned to the centre on the evening of day 9, and remained resident until discharge on the morning of day 11 of each period.

Pharmacokinetic sampling

Blood samples (5 ml) were taken predose on the morning of days 1–9 for the determination of trough plasma voriconazole concentrations and at regular intervals up to 24 h and 12 h after dosing on days 1 and 10, respectively, for the determination of plasma voriconazole concentrations.

Blood was collected in heparinized tubes, centrifuged at 1500 *g* at 4 °C for 10 min within 1 h of collection, and the plasma stored upright in screw-capped polypropylene tubes at −20 °C, pending assay.

Plasma assays

Plasma voriconazole samples were assayed using a previously validated high-performance liquid chromatography assay [20] (BAS Analytics Ltd, Stareton, UK). Over the calibration range 25–4805 ng ml^{-1}, the overall imprecision and inaccuracy of the assay were 3.6–8.9% and −0.4–5.4%, respectively. The lower limit of quantification was 10 ng ml^{-1}.

Pharmacokinetic analysis

The maximum observed plasma concentration (C_{max}) and the time to the first occurrence of C_{max} (t_{max}) were

obtained directly from the plasma concentration–time curves. The area under the plasma concentration–time curve over the dosing interval (AUC_τ) was determined using the linear trapezoidal method. Attainment of steady-state concentrations of voriconazole for both the omeprazole and placebo groups was confirmed by visual inspection of predose plasma concentrations (C_{min}).

Safety assessments

Safety assessments were repeated throughout the study, from screening (up to 3 weeks prior to first dose), until follow-up (7–10 days post final dose). Assessments included physical examination (supine blood pressure and pulse rate, ophthalmological tests), liver function tests, and routine haematological and urinary analyses. A 12-lead electrocardiogram (ECG) was recorded at screening and follow-up.

All adverse events that occurred during treatment, or up to 30 days post final dose, were documented, together with their severity, time of onset and duration, and the investigator's assessment of their relationship to treatment. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing conditions were recorded. Objective test findings that resulted in dosage change or discontinuation were also recorded as adverse events. All adverse events were followed up until their sequelae had resolved or stabilized satisfactorily.

Statistical analysis

Log-transformed AUC_τ and C_{max} and untransformed t_{max} for day 1 (following the first and second doses) and day 10 were subjected to an analysis of variance (ANOVA) which allowed for variation due to sequence, subject within sequence, period and treatment. Separate analyses were performed for each of these three assessment times. The mean differences between treatments were estimated along with their 90% confidence intervals (CI). The ratio between antilogged treatment means and the corresponding antilogged CIs were presented. Steady state was visually assessed using the C_{min} data. Laboratory and other safety data were not subjected to formal statistical analysis. All analyses and tabulations were performed using SAS/STAT® (SAS Institute Inc., North Carolina, USA) software [21].

In order to take account of potential dropouts, a total of 18 subjects were recruited into the study with the intention of at least 16 subjects completing the study. With a sample size of 16 subjects the two-sided test at the 5% significance level had 80% power of detecting a difference between the treatments, assuming the true increase in C_{max} and AUC_τ was at least 20%. The calculation was based on data from a previous study (Pfizer Inc., data on file), where the within-subject coefficients of variation for C_{max} and AUC_τ were estimated as 18% and 11%, respectively.

Results

Subjects

Eighteen subjects were enrolled in the study, and randomized to treatment. The mean age of the subjects was 26.3 years (range 20–40 years), mean weight was 75.1 kg (range 66.3–92.0 kg), and mean height was 179.8 cm (range 168.0–190.0 cm). One subject discontinued on day 8 of the voriconazole + omeprazole study period due to elevated liver function test results and did not start the voriconazole + placebo phase. Thus, all 18 subjects were included in the safety assessment for voriconazole + omeprazole whereas only the 17 subjects who completed all study assessments were included in the safety analyses during the voriconazole + placebo phase, and in the pharmacokinetic analyses. Genotyping of the CYP2C19 locus indicated that three subjects were CYP2C19 PMs, 14 were homozygous EMs, and one was a heterozygous extensive metabolizer (HEM).

Pharmacokinetics

The pharmacokinetics of the oral loading dose regimen of 400 mg voriconazole twice daily on day 1 were not influenced by the concomitant administration of omeprazole (Figure 1). Compared with the voriconazole + placebo period, geometric mean ratios (voriconazole + omeprazole/voriconazole + placebo) of C_{max} were 93% (90% CI 85, 102) and 101% (88, 116), and of AUC_τ were 101% (91, 111) and 118% (105, 132), after the first and second loading doses of voriconazole, respectively (Table 1).

Visual inspection of the mean C_{min} data indicated that steady-state voriconazole plasma concentrations were achieved following administration of the second oral loading dose of 400 mg, and maintained until day 10 in both treatment groups (Figure 2). The mean C_{min} plasma voriconazole concentrations were observed to be higher in the voriconazole + omeprazole period than in the voriconazole + placebo period.

At steady-state plasma concentrations of voriconazole on day 10, C_{max} and AUC_τ were higher in the voriconazole + omeprazole period than in the voriconazole + placebo phase, with ratios of geometric means of 115% (90% CI 105, 125) and 141% (129, 155), respectively (Table 1). Omeprazole had no effect on the T_{max} of voriconazole.

Inspection of the individual subject data on days 1 and 10 revealed that the two PM subjects who completed the study had higher plasma concentrations of

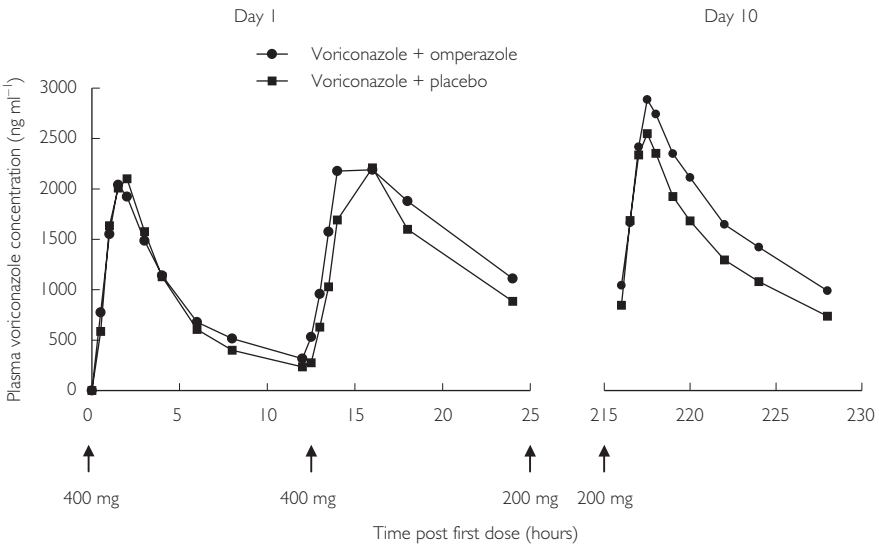

Figure 1 Mean plasma concentrations of voriconazole on day 1 following administration of 400 mg twice-daily loading doses and at steady state on day 10.

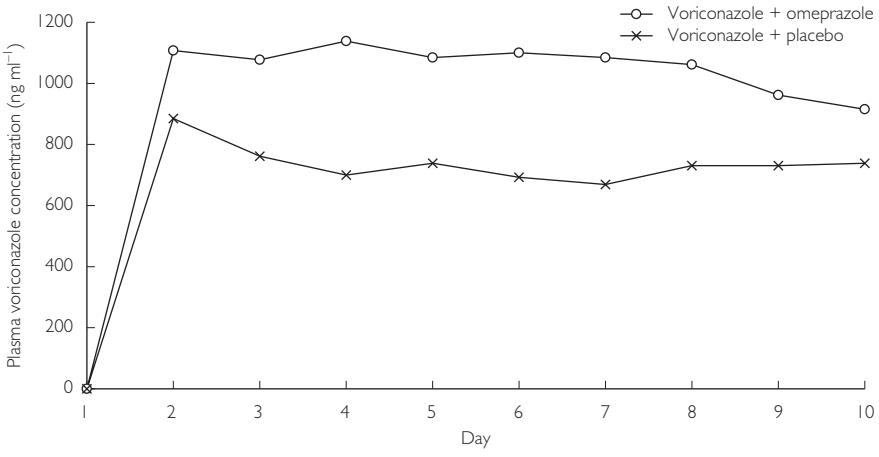

Figure 2 Trough plasma concentrations of voriconazole, days 1–10.

Table 1 Statistical comparison of mean pharmacokinetic parameters for voriconazole in plasma on days 1 and 10.

Time	*Parameter*	*Voriconazole + omeprazole*	*Voriconazole + placebo*	*Difference/ratio between means* (90% CI)*
Day 1 (1)†	C_{max} (ng ml^{-1})‡	2 147 (24)	2 305 (19)	93% (85, 102)
	AUC_τ (ng·h ml^{-1})‡	9 353 (42)	9 305 (38)	101% (91, 111)
	t_{max} (h)§	1.6 ± 0.4	1.6 ± 0.4	0.01 (– 0.18, 0.19)
Day 1 (2)†	C_{max} (ng ml^{-1})‡	2 358 (40)	2 329 (35)	101% (88, 116)
	AUC_τ (ng·h ml^{-1})‡	19 191 (45)	16 290 (52)	118% (105, 132)
	t_{max} (h)§	15.4 ± 1.6	15.1 ± 1.1	0.24 (– 0.45, 0.92)
Day 10	C_{max} (ng ml^{-1})‡	2 387 (47)	2 083 (62)	115% (105, 125)
	AUC_τ (ng·h ml^{-1})‡	15 771 (65)	11 153 (103)	141% (129, 155)
	t_{max} (h)§	1.5 ± 0.4	1.4 ± 0.3	0.12 (– 0.07, 0.30)

*Ratio (%) between means shown for C_{max} and AUC_τ, difference between means for t_{max}. †Day 1 (1), day 1, first dose. Day 1 (2), day 1, second dose. ‡Geometric mean with coefficient of variation (%) in parentheses. §Arithmetic mean ± s.d.

Table 2 Numbers of subjects reporting treatment emergent adverse events (all causalities).

	Voriconazole + omeprazole (n = *18*)	*Voriconazole + placebo* (n = *17*)
Number of subjects with adverse events	14	15
Number of adverse events	32	27
Visual adverse events	9 (2)*	11
Enhanced/altered visual perception	8	6
Blurred vision	3	1
Photophobia	3	4
Other	1	0

*Values in parentheses indicate number of severe adverse events.

voriconazole than the EMs during both treatment phases. Their omeprazole/placebo treatment ratios on day 10 were 82% and 92% for C_{max} and 80% and 101% for AUC_τ, respectively.

Safety and toleration

One PM subject was discontinued from the study on day 8 while receiving voriconazole + omeprazole, due to elevated liver function test results (AST and ALT >2 × upper limits of normal), thought to be treatment related. Values of 123 IU l^{-1} and 166 IU l^{-1} were recorded on days 8 and 10 for AST and ALT, respectively. These compared with baseline values of 24 IU l^{-1} for AST and 28 IU l^{-1} for ALT. Following discontinuation of treatment, both AST and ALT were within the normal range by study day 17 (9 days after the last dose).

The numbers of subjects reporting treatment-emergent adverse events of all causality, 14 in the voriconazole + omeprazole period and 15 in the voriconazole + placebo period, and the number of adverse events reported were similar in the two treatment periods (Table 2). The most common treatment-emergent treatment-related adverse events were headache, abnormal vision, and photophobia. Three adverse events were classified as severe in the voriconazole + omeprazole period (one instance of abnormal liver function test results and two of abnormal vision) and one adverse event (headache) was classified as severe in the voriconazole + placebo period, although the latter was not attributed to the study drug by the investigators. Apart from the subject who discontinued treatment on day 8, all adverse events resolved without intervention.

Visual adverse events were reported by nine subjects receiving voriconazole + omeprazole and 11 subjects receiving voriconazole + placebo (Table 2). For the two study phases, median times to onset for these events were 18 min (range 2–752 min) and 32 min (range 3–690 min), and median durations were 28 min (5–660 min) and 15 min (5–120 min), respectively.

Discussion

Coadministration of omeprazole had little effect on the systemic exposure to voriconazole following administration of two oral loading doses of 400 mg voriconazole on day 1. AUC_τ was increased by 18% compared with placebo following administration of the second loading dose. However, at steady-state plasma concentrations of voriconazole, following administration of a 200-mg bid maintenance regimen, day 10 mean C_{max} and AUC_τ values increased by 15% and 41%, respectively, compared with placebo. Considering the normal interindividual variations in voriconazole pharmacokinetics observed in this (Table 1) and previous pharmacokinetic studies [22], these increases are considered unlikely to be of clinical significance. Omeprazole had no effect on voriconazole t_{max}. Systemic voriconazole exposure was not increased by omeprazole in the two PM subjects who completed the study. This finding is consistent with the absence of the *CYP2C19* gene in these subjects.

This study was designed to determine the effects of omeprazole on the steady-state pharmacokinetics of voriconazole. However, an effect of voriconazole on the metabolism of omeprazole cannot be excluded, since the metabolism of omeprazole is mediated mainly by CYP2C19 and CYP3A [16, 17] and voriconazole is metabolized by CYP2C19, CYP2C9 and, to a lesser extent, by CYP3A4 [9]. A study to examine the effects of multiple oral doses of voriconazole on the pharmacokinetics of omeprazole and its metabolites 5-hydroxy omeprazole and omeprazole-sulphone has been conducted and will be reported separately.

The loading dose regimen of 400 mg voriconazole twice daily on day 1 resulted in steady-state plasma concentrations being achieved following administration of the second loading dose, which were maintained throughout the dosing interval of 10 days with the 200-mg b.d. maintenance regimen. The mean voriconazole C_{min} values following coadministration of voriconazole + omeprazole were observed to be higher than those fol-

lowing voriconazole + placebo; however, the difference is considered unlikely to be clinically relevant.

Treatment-related adverse events were generally mild or moderate in severity and the majority of events were transient and resolved without intervention. The adverse event rate was comparable to previous studies in healthy volunteers [22]. One PM subject was withdrawn when voriconazole was coadministered with omeprazole, due to elevated liver function test values. However, following discontinuation of study drug, the abnormalities resolved without intervention by the time of the follow-up visit.

It can be concluded from the present study that, with the dosing regimens described, combination treatment with omeprazole and voriconazole is generally well tolerated. Multiple doses of omeprazole were observed to increase the systemic exposure to voriconazole at steady state, but the increases are considered unlikely to be of clinical relevance and are considered insufficient to warrant dosage adjustments. In addition, the pharmacokinetic profile of a 400-mg twice-daily oral loading dose was examined and resulted in steady-state plasma levels of voriconazole being achieved following the second loading dose.

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